New York State Department of Health

Clinical Guidelines
for the Medical Management of Hepatitis C

2005

Appendices

A. Introduction

Hepatitis C virus (HCV) infection is a major public health problem, a leading cause of chronic liver disease throughout the world, and the leading cause of death from liver disease in the United States (U.S.). [1] In New York State (including New York City), there are an estimated 237,000 people with chronic hepatitis C (CHC) based on surveys from the Centers for Disease Control and Prevention (CDC). These estimates of prevalence are likely conservative, because they do not include incarcerated and homeless persons, groups that have a high prevalence of HCV infection.

HCV infection is a reportable disease in New York State (10NYCRR2.1). In the past, reporting guidelines have emphasized the reporting of new acute cases of HCV; however, as of 2002, reporting guidelines require the reporting of both new acute and chronic HCV cases. Furthermore, in January 2003, CDC made CHC a nationally reportable disease and since then, the New York State Department of Health (NYSDOH) is submitting all reported cases of CHC to CDC on a weekly basis.

CHC accounts for at least 40% of liver transplants in the U.S. today and the number of HCV-infected patients with cirrhosis is estimated to double over the next 20 years.[1] Identifying and treating patients with bridging fibrosis or cirrhosis on liver biopsy best accomplish reduction in complications of cirrhosis. Although antiviral treatment with interferon-based regimens is successful in many patients, this treatment may be complex to administer and requires careful patient monitoring for the occurrence of adverse events and dose adjustments, as needed, as well as experienced providers to manage patient care. [2]

In 2004, the NYSDOH convened a panel of experts in the field of HCV medical care, and consumers to develop these guidelines. The purpose of the guidelines is to provide clinicians with practical, state-of-the-art information on the diagnosis, medical management, and prevention of HCV infection. These guidelines are intended for the medical management of adults and children infected with HCV. While the field of HCV medicine is still evolving, these guidelines review the currently available evidence to support the recommendations, and, where published data are lacking, present standards of care as recommended by the panel.

The final guidelines will be presented in two formats: (1) a condensed version with recommendations and tables and figures, and (2) the full version that includes rationale for the recommendations, appendices, and references.

B. Epidemiology and Natural History

It is estimated that 170 million people worldwide are chronically infected with HCV, known as non-A, non-B hepatitis prior to 1989. [3] HCV is the most common chronic blood-borne infection in the U.S.[4] The Third National Health and Nutrition Examination Survey (NHANES III) showed that the prevalence of antibody to HCV (anti-HCV) in the U.S. is 1.8% or approximately 4 million people.[5] Seventy-four percent of these (i.e., an estimated 2.7 million people) are also positive for HCV RNA, and considered chronically infected. [6]

The incidence of HCV infection in the U.S. began rising in the 1960's, peaked in the late 1980's, and began declining in the 1990's. In 2001, the annual infection rate was 25,000 new cases per year. [7] However, the occurrence of symptomatic CHC among people initially infected in the 1970's and 1980's could increase significantly over the next 10 years, peaking around 2015.[4] For example, the age-adjusted death rate for "non-A, non-B" viral hepatitis increased from 0.4 to 1.8 deaths per 100,000 persons per year between 1982 and 1999. In 1999, the first year hepatitis C was reported separately in the U.S., there were 3,759 deaths attributed to HCV, although this is likely an underestimate. In 1998, an estimated 140,000 hospital discharges listed an HCV-related diagnosis, accounting for 2% of discharges from non-federal acute care hospitals in the U.S. There was a five-fold increase in the annual number of patients with HCV who

underwent liver transplantation between 1990 and 2000 and, currently, more than one third of liver transplant candidates have HCV. [1]

The incidence of new cases of HCV infection in the U.S. is declining. However, the disease burden of HCV infection is projected to continue to rise in the U.S. in the foreseeable future with a four-fold increase between 1990 and 2015 in persons at risk of chronic liver disease (i.e., those with infection for 20 years or longer) . [1, 8] In a detailed analysis, Leigh et al. estimated that the costs of HCV in the U.S. in 1997 were $5.46 billion. Of this amount, direct costs, defined as inpatient and outpatient medical care and administrative expenses, accounted for $1.8 billion (33%). Indirect costs, defined as lost wages, benefits and productivity, accounted for the remainder. [8]

The prevalence of HCV infection in the U.S. is higher among African-Americans (3.2%) and Hispanics (2.1%) than among non-Hispanic Caucasians (1.5%). In the general population, males have higher prevalence rates than females (2.5% and 1.2%, respectively); however, in incarcerated populations the reverse has been seen. The strongest factors independently associated with HCV infection are injection drug use (IDU) and, to a lesser extent, high-risk sexual behavior. Higher prevalence rates have been observed in people who are divorced or separated, people living in poverty, people who have had 12 years or less of education, people receiving hemodialysis, and people who have had a solid organ transplantation. In addition, higher prevalence rates may be seen following HSV-2 infection or blood transfusion, and with perinatal exposure. [3,6,9]

The seroprevalence of antibodies to HCV is approximately 0.2% in children less than 12 years of age and 0.4% in those 12 to 19 years of age. In several studies, viremia occurs in 50-75% of antibody-positive children. Spontaneous HCV clearance appears to occur more commonly in children, particularly during the first year after infection. [10]

Certain subpopulations in the U.S. have HCV infection prevalence rates higher than that seen in the general population. These include inmates entering correctional facilities (in New York State, 13.3% in males and 24% in females; 23.1% in Rhode Island; 29.7% in Maryland; and, in Texas, 29.7% among males, and 48.6% among females), and homeless men (50%). [9,11-14]

In the U.S. and other western countries, and in Japan, most HCV-infected people have genotypes 1, 2 or 3. In the U.S., 73.7% of chronically infected individuals have genotype 1. Elsewhere in the world, other genotypes are prevalent, and may even predominate: genotype 4 in Africa and the Middle East; genotype 5 in South Africa; genotypes 6 to 9 in southern China and Southeast Asia; and genotypes 10 and 11 in Indonesia. [6,15]

Acute HCV infection is often asymptomatic or presents with non-specific symptoms. Jaundice occurs in only about 25% of cases. As a result, acute infection is not easily recognized and few patients come to medical attention. Spontaneous resolution occurs in up to 25% of patients; hence, the majority of patients become chronically infected with persistent viremia. [3]

Once chronic infection is established, it is unlikely that spontaneous clearing will occur. [16] Spontaneous clearance of acute HCV infection occurs more frequently with genotype 3 compared to genotype 1, with clearance rates of 37% and 7%, respectively. [17] Spontaneous resolution occurs less frequently with co-infection with human immunodeficiency virus (HIV), and with excessive alcohol use. [18]

Co-infection with HIV and hepatitis is common, especially in areas with high proportions of IDU. Nationally, approximately 30% of people infected with HIV are estimated to be co-infected with HCV, and 50% -90% of people who acquired HIV through injection drug use (IDU) are co-infected with HCV. Further recommendations for the HIV/ HCV co-infected patient are provided at: www.hivguidelines.org/public_html/hep-c/adl-hepc.htm

C. Risk Assessment and Screening

Recommendations

Persons at increased risk for HCV infection should be screened for serum HCV antibody.

HCV testing should be available to any patient who requests it.

Approximately 90% of patients with HCV have identifiable risk factors for infection. Understanding the relative risk for HCV infection is helpful for patient selection for screening (see Table 1).

Table 1

Relative Risk Factors for Hepatitis C Transmission

High Risk

- Injection drug use
- Blood or blood product transfusion or transplantation prior to 1992

Moderate Risk

- High-risk sexual activity*
- Vertical transmission from mother to baby

Low risk

- Occupational exposure
- Sexual activity between long-term spouses/ sexual partners

Very low/No risk

- Casual contact
- Household contact

*Sexual transmission of HCV is not clearly understood. However, certain high risk sexual behaviors have been associated with HCV transmission such as anal sex, sex with trauma, sex in the presence of a sexually transmitted disease (STD), and sex without a condom.

HCV is transmitted primarily through percutaneous exposure to infected blood. At least two-thirds of the patients currently identified with CHC infection were infected through injection drug use. [19] Transfusion of blood or blood products is also strongly associated with the transmission of HCV. Although transmission of HCV by transfusion has declined dramatically in the U.S. following the introduction of more sensitive serological tests for HCV in 1992, some patients transfused before adequate screening was available are still being identified. [19]

The sexual transmission of HCV is not clearly understood. HCV is transmitted uncommonly between long-term spouses/ sexual partners, with an average prevalence of 1.5%. [19] Men who have sex with men (who do not engage in IDU) do not appear to be at substantially increased risk compared to controls. [21] However, hepatitis C is more prevalent among those with multiple sex partners, a history of STDs, and/or failure to use a condom. [19,22-24] In contrast, transmission via non-sexual household contact is rare in the U.S. and there is no evidence to suggest that HCV is transmitted by casual contact such as hand shaking, kissing, or sharing eating utensils. [19, 25] HIV and HCV share similar modes of transmission. The overall frequency of those with HIV being co-infected with HCV ranges from 16% to 30%, depending on the population studied. [26,27] The overall rate of co-infection in those with HIV living New York City, is estimated to be 40%, with much higher rates among those with IDU as a risk factor for HIV.

Overall, the vertical transmission rate is approximately 5% (3-7% when the mother is only infected with HCV), and is not influenced by the method of delivery.[28] The transmission rate of HCV is higher when the mother has a higher HCV RNA and when the mother is also co-infected with HIV.[29] It is important to note that HCV antibodies may be transmitted passively from mother to baby. Thus, many children born to HCV-infected mothers will have passive antibody that may persist up to 18 months following delivery, but will not become infected with HCV. Therefore, testing for HCV antibody may be deferred until after 18 months of age. If

there is a need for earlier diagnosis, HCV RNA may be measured at one to two months of age, at the time of the child's first well-child visit. [30,31] Breast-feeding does not appear to be a significant risk factor, and should not be discouraged unless the nipples are cracked or bleeding. [30]

Transmission of HCV from patients to healthcare workers has been reported but is uncommon and the prevalence of hepatitis C in healthcare workers is similar to the general population. [19,32] Seroconversion following accidental needle puncture is also uncommon and appears to be approximately 2% with a range of 0-7% .[19,33] The exposure of mucous membranes or intact skin to infected blood does not appear to be a factor for transmission of HCV. Although rare, HCV transmission from infected healthcare workers to patients has been reported.[34,35]

While there is neither a standard approach nor definitive guidelines for management of occupational exposures or infected healthcare providers, this document provides some guidance for post-HCV exposure management (Section G). Although the NYSDOH does not address HCV specifically in policies for prevention of transmission of bloodborne pathogens, an existing policy statement does address prevention of exposure to HIV, hepatitis B virus (HBV), and other bloodborne pathogens, balanced against the rights of infected workers

(Appendix B). HIV or HBV infection alone does not justify limiting a healthcare worker's professional duties. [36] Limitations, if any, should be determined on a case-by-case basis after consideration of the factors that influence transmission risk, including inability or unwillingness to comply with infection control standards or functional impairment which interferes with job performance. The policy statement also requires the use of standard precautions and infection control training for licensed healthcare professionals every four years.

Up to 10% of those infected with HCV have no identified risk factor for acquisition of the virus. These patients may not recall past exposures, or may be reluctant to report risk factors. Intranasal cocaine use, tattoo application, religious scarification and body piercing have been associated with HCV infection. [19]

Finally, the guidelines panel's opinion is that HCV testing should be available to any patient who requests it. However, there is insufficient evidence to support routine screening in asymptomatic persons not at increased risk for HCV infection, according to the U.S. Preventive Services Task Force (USPSTF). In this group, the risks of screening and the subsequent diagnostic testing, if positive, may have risks outweighing the benefits.[37]

D. Diagnosis

1. Testing for HCV Infection

The recommendations for testing are derived from published evidence and expert opinions.[22,23] There are many options for HCV testing and, as newer diagnostic technologies are introduced, HCV testing should become more streamlined. Also, some providers will have limited choices for testing because of laboratory testing protocols and reimbursement issues. Providers are advised to consult with their laboratories for information regarding available tests and testing protocols.

Recommendations

All patients suspected of having infection with HCV should be tested for antibody to HCV (anti-HCV) using an EIA (enzyme immunoassay) screening test.

In low-risk patients with a positive EIA test, confirmatory testing with the recombinant immunoblot assay (RIBA) should be performed.

For patients at low risk with a positive EIA and RIBA, confirmatory testing with a qualitative PCR test for detection of HCV RNA should be performed.

For patients at moderate or high risk and/ or unexplained elevated serum alanine aminotransferase (ALT) value, a positive EIA should be followed by a qualitative test for HCV RNA in the blood.

For immunocompromised patients at high risk with unexplained elevated ALT value and a negative screening EIA, a qualitative test for detection of HCV RNA should be performed to diagnose HCV infection.

There is no recommendation for serial or periodic screening unless there has been repeat or ongoing high-risk behavior.

Quantitative PCR HCV RNA tests should be obtained for patients who are candidates for antiviral therapy.

2. Testing for Chronic HCV Infection

The initial screening test to be used in all circumstances is a test for antibody to hepatitis C viral proteins (anti-HCV). These tests become positive as early as 8-10 weeks after infection, will be positive in 97% of patients by 6 months after infection, and probably will persist for life. Presence of anti-HCV does not define activity of infection. Up to 25% of patients will resolve infection spontaneously, but will still have detectable anti-HCV. Antibody tests currently recommended for anti-HCV screening include the EIA test and the more specific RIBA; the latter being used to confirm a positive EIA test in some situations (e.g., confirming EIA positivity in low-risk patients). These antibody tests are highly reliable for determining HCV infection at some time in the past.

Detection of HCV RNA in blood is the currently accepted "gold standard" for diagnosis of active HCV infection. Tests for HCV RNA are both qualitative and quantitative, vary in technical aspects, and report values differently.

3. Characteristics of Antibody Tests for the Diagnosis of Chronic HCV Infection

Currently available EIA tests are highly sensitive and useful for screening. However, among a population with low risk, even a highly sensitive test does not provide the desired predictive value of a positive test. The lower the likelihood of infection, the higher the risk of a false positive test. Conversely, the higher the risk of hepatitis C in the population, the greater the likelihood that a positive screening EIA test indicates infection. In populations with otherwise unexplained ALT elevation and at least one major risk factor for hepatitis C, the positive predictive value of a positive EIA is at least 95%. This value declines to less than 50% for patients with normal ALT levels and minimal or no risk factors. [38]

Two strategies have been employed to decrease the possibility of "false positive" EIA tests:

- Recalibration of the EIA test value called "positive" has allowed a higher degree of positive prediction for the test in general. This gives the EIA test excellent characteristics for use in appropriate populations, and simplifies the use of confirmatory tests.

- Confirmatory testing for more specific antibody to hepatitis C virus. The recommended test is the RIBA to confirm a positive EIA test in a patient with low risk for hepatitis C.

A relatively small fraction of the population perceived to be at risk might have a false negative screening test. These populations include patients with advanced HIV, hemodialysis patients and patients with profound immunosuppression due to solid organ transplantation. [39] Also included, are patients infected and screened soon after exposure when an antibody response has not been mounted to detectable levels. When other clinical or laboratory findings support a possible diagnosis of hepatitis C, qualitative testing for HCV RNA by PCR or transcription mediated assay (TMA) is appropriate. (see Table 2).

4. Testing for Acute Hepatitis C

Between 1-8 weeks after transmission of hepatitis C, HCV RNA becomes detectable by PCR testing. Although most patients will have some liver function test (LFT) abnormalities from 6-12 weeks after transmission, only about a quarter will have the syndrome of malaise, abdominal pain, and jaundice that characterizes acute hepatitis C disease. By 12 weeks after development of hepatitis C viremia, up to 25% of patients will spontaneously and permanently clear the virus. [40] Spontaneous clearance appears to be much more common in those with the syndrome of acute hepatitis C than in those with asymptomatic viremia. [41] Development of hepatitis C antibodies occurs as early as 8-10 weeks after transmission.[42] Some immunosuppressed individuals may not develop hepatitis C antibodies despite the presence of viremia. [43]

Table 2

HCV RNA Tests
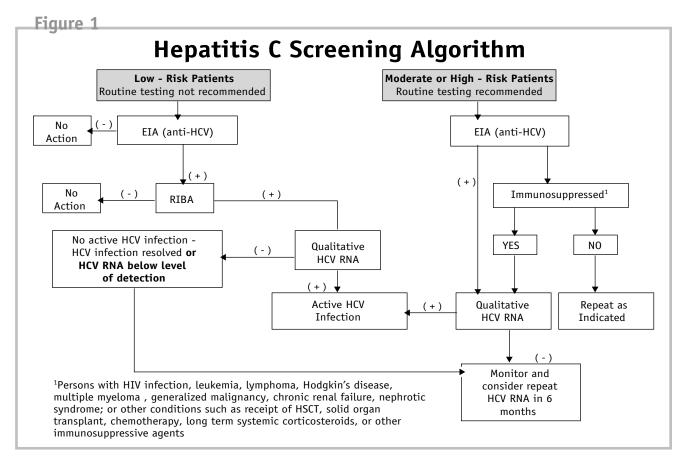
Qualitative	Method; Manufacturer	Dynamic Range (IU/ mL)*
Amplicor HCV test 2.0	PCR; Roche	≥ 50
COBAS Amplicor HCV test 2.0	PCR; Roche	≥ 50
VERSANT HCV RNA Assay	TMA; Bayer	≥ 5
Quantitative		
Versant™ HCV RNA 3.0	bDNA; Bayer	$615 - 77.7 \times 10^6$
§COBAS Amplicor HCV Monitor™	qPCR; Roche	$600 - 7 \times 10^5$
COBAS TaqMan™ HCV	qPCR; Roche	$10 - 2 \times 10^8$
Celera HCV QT ASR	qPCR; Abbott	$25 - 5 \times 10^8$

*Results may vary at the lower limit of detection depending on the laboratory performing the test

§Research Use Only- Not approved for patient use

bDNA: branched chain DNA

PCR: polymerase chain reaction

qPCR: quantitative polymerase chain reaction

TMA: transcription mediated assay

ASR: analyte specific reagent

The use of proprietary names does not constitute endorsement by the NYS DOH.

5. Summary of Available Tests for HCV Screening

A comparison of currently available tests for HCV RNA is shown in Table 2 and a testing algorithm is shown in Figure 1.

- EIA is a reproducible and inexpensive test suitable for screening. This test identifies if there is antibody to HCV present. The currently available third generation tests have a high specificity and sensitivity of greater than 99%. [22,23] The high sensitivity and specificity may obviate the need for a confirmatory immunoblot assay in the patient with clinical liver disease, especially in high-risk patients for HCV.

- RIBA determines if there is antibody to the HCV present. This test is very sensitive and reliable, and can be used as a confirmatory test of the EIA. A positive RIBA is not diagnostic of active HCV infection since up to 25% of patients will clear HCV spontaneously after acute infection yet remain anti-HCV positive. The diagnosis of active HCV infection requires additional testing.

- PCR testing is used to determine the presence of HCV RNA and is an indication of active infection. There are two types of PCR tests, commonly called viral load tests: qualitative and quantitative (see Table 2).

  - Qualitative PCR or TMA testing determines if HCV is present or not. Traditionally, qualitative tests have been more sensitive with a lower limit of detection of 5 IU/ mL. Qualitative test results are reported as positive or negative and are not reported numerically. A single negative qualitative test does not exclude viremia, since viral load can have transient declines. The negative test may reflect that the viral load was below assay detection at that particular point in time.

  - Quantitative PCR determines the amount of virus present. The lower limit of detection for earlier versions of these tests has been around 600 IU/ mL. More recent versions are more sensitive with a broader dynamic range from around 5-25 IU/mL to $> 10^8$ IU/mL, depending on the laboratory.

Figure 1

Hepatitis C Screening Algorithm

[Low - Risk Patients: Routine testing not recommended]
- EIA (anti-HCV) → (-) → No Action
- EIA (anti-HCV) → (+) → RIBA
  - RIBA → (-) → No Action
  - RIBA → (+) → Qualitative HCV RNA
    - Qualitative HCV RNA → (-) → No active HCV infection - HCV infection resolved **or HCV RNA below level of detection**
    - Qualitative HCV RNA → (+) → Active HCV Infection

[Moderate or High - Risk Patients: Routine testing recommended]
- EIA (anti-HCV)
  - (+) → Immunosuppressed[1]
    - YES → Qualitative HCV RNA
    - NO → Repeat as Indicated
  - Qualitative HCV RNA → (+) → Active HCV Infection
  - Qualitative HCV RNA → (-) → Monitor and consider repeat HCV RNA in 6 months

[1]Persons with HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma , generalized malignancy, chronic renal failure, nephrotic syndrome; or other conditions such as receipt of HSCT, solid organ transplant, chemotherapy, long term systemic corticosteroids, or other immunosuppressive agents

These newer technologies may help streamline the testing process when used for confirmation of anti-HCV, therapeutic monitoring and test of cure.

- Genotype testing is widely available and is useful in treatment planning and for determining length and possible responses to treatment. Genotype testing should be done as part of the patient's initial evaluation once CHC has been confirmed.

- Liver chemistries, though inexpensive, are an insensitive means of assessing disease activity. Elevations of ALT and aspartate aminotransferase (AST) may indicate the presence of liver disease, but do not determine the type of liver disease, what has caused it, or the degree of damage to the liver.

6. Liver Biopsy

Recommendations

In patients with genotype 1 or 4, pre-treatment liver biopsy should be performed to assess the likelihood of a sustained virologic response(SVR).

In patients with genotype 2 or 3, it may not be necessary to perform a liver biopsy.

Liver biopsy remains the only definitive test for evaluation of fibrosis stage, and fibrosis stage is the most reliable means to assess prognosis and provide information for decisions about the need for initiation of therapy. Because up to 80% of patients with HCV genotype 2 or 3 disease respond favorably to antiviral therapy, a decision to treat is more straightforward, and a pretreatment liver biopsy might not be necessary for those with genotype 2 or 3 disease. If performed, liver biopsies should be evaluated by pathologists with training and experience in hepatic histology.

A liver biopsy was regarded as an important parameter in helping to guide management and treatment, particularly at a time when response to treatment was low. More recently, with the improvement of treatment effectiveness, the value of the liver biopsy

has been questioned because of the potential risks of the procedure and the concern of sampling error. This has prompted some to challenge the need for biopsy and to suggest that the procedure may not be necessary prior to treatment. At the present time, the American Association for the Study of Liver Disease (AASLD) recommends that regardless of the level of ALT, a liver biopsy should be done when the results will influence whether treatment is recommended. A biopsy, however, is not mandatory in order to initiate therapy. [22]

7. Noninvasive Testing to Assess Liver Fibrosis

Recommendation

The use of non-invasive tests to assess liver fibrosis is not yet recommended.

Various non-invasive tests are being investigated for staging degree of liver fibrosis. These tests may be used in decisions regarding whether or not to initiate antiviral therapy and to monitor the effects of such therapy. [44] An array of such tests would be highly desirable if adequately validated, since liver biopsy may not be readily available in view of the large number of affected patients with hepatitis C, the risks involved in performing liver biopsies, and the problem of sampling error on biopsy that can underestimate cirrhosis in 10-30% of cases.

Standard liver biochemical tests, measures of liver function such as coagulation studies, and radiological imaging of the liver may be sufficiently sensitive to diagnose advanced cirrhosis but have not been accurate in defining evolving hepatic fibrosis and early stages of cirrhosis.[44] A number of studies have been published employing a variety of indirect markers of liver fibrosis (Fibrosure and Fibrostat) including standard liver chemistries, platelet count, prothrombin index, and lipoprotein A1 concentrations. These tests have gained acceptance in Europe as alternatives to liver biopsy. [45,46] However, the utility of these tests requires further validation in prospective studies.

Direct markers of liver fibrosis are also being evaluated, including a number of

serum or urinary tests, which are thought to directly reflect the deposition or removal of extracellular matrix involved in formation of fibrous tissue in the liver.[44] Similar to indirect markers, these tests, such as assays for type IV collagen and hyaluronic acid, may be able to identify patients with significant fibrosis and cirrhosis. Patients with early fibrosis may also be identified. However, the limitation of both direct and indirect serological markers remains the inability to accurately define intermediate stages of hepatic fibrosis.[44]

Ongoing studies should help resolve this issue and put these studies in the proper context for management of patients with hepatitis C. Adequate standardization and availability of these tests will be required before they will be of value to the clinician in making decisions as to the need for liver biopsy and to begin or discontinue therapy. Future work must define an ideal algorithm for optimal use of serologic test or tests for incorporation into clinical practice. With proper validation, it is possible that such tests may be equal to or superior to liver biopsy in assessing the degree of hepatic fibrosis.

8. Screening for Hepatocellular Carcinoma

Recommendation

Patient with cirrhosis should be screened for hepatocellular carcinoma (HCC) with alpha-fetoprotein (AFP) testing and hepatic ultrasound imaging at least once yearly.

Hepatitis C is the most common predisposing factor for the development of HCC in the U.S.[47,48] Resection and local ablative treatments have long been used to treat patients with HCC. Liver transplantation is increasingly an option for patients with early HCC who are not likely to benefit from surgical resection.[49] Despite these therapies, which are achieving some success, screening
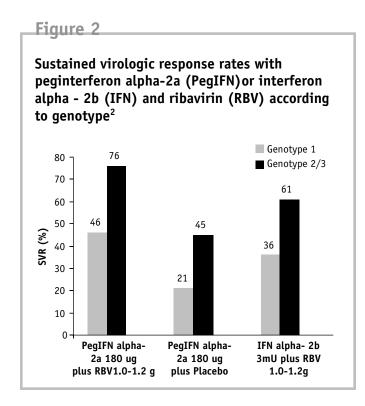
for HCC is controversial.[50] Screening is most commonly performed with regular imaging by ultrasonography or CT-scan, and serum AFP determination. AFP testing alone has relatively low sensitivity and specificity for HCC. In a recent study of 357 patients with CHC but not HCC, 23% had an elevated serum AFP level that was independently associated with stage III/IV hepatic fibrosis, elevated level of AST, and prolonged International Normalized Ratio (INR).[51]

Hepatic ultrasound has greater sensitivity than AFP testing but is associated with significant rate of false positive results, particularly in the setting of regenerative nodules associated with cirrhosis. There is emerging evidence from a small number of studies that screening for HCC improves survival. For example, a prospective randomized trial conducted in China and a retrospective analysis of cirrhotic patients with chronic liver disease in Italy showed that survival was improved by surveillance for HCC probably because tumors were identified at an earlier stage.[52,53] However, the etiology of cirrhosis in these studies was heterogeneous. At present, despite the lack of firm evidence for efficacy of surveillance, it remains standard practice to screen for HCC with AFP testing and hepatic ultrasound imaging; however, the optimal interval for screening remains undetermined. A recent study indicates that biannual AFP/ annual ultrasonography is cost effective.[54] There is great need for more sensitive and specific screening tests. Consideration should also be given to whether a patient undergoing screening can be expected to benefit from and tolerate treatment of HCC. Further studies are required to better define the reliability, benefits, as well as the standard of care for frequency of screening for HCC.

E. Treatment of Hepatitis C

The primary goal of HCV therapy is to achieve a SVR, defined as an undetectable HCV RNA 6 months after stopping antiviral therapy. Secondary goals of antiviral therapy include improvements in histology, quality of life and prevention of hepatocellular carcinoma. Antiviral therapy is approved by the Food and Drug Administration (FDA) for patients with persistently abnormal liver enzymes, detectable HCV RNA and an abnormal liver biopsy. Recent data have shown that patients with normal liver enzymes, detectable HCV RNA and an abnormal liver biopsy respond to therapy at similar rates as those with abnormal liver enzymes. [55]

The efficacy of HCV treatment has improved over the past decade. Initial treatment consisting of interferon alpha has been replaced by pegylated interferon and now by combination therapy using pegylated interferon and ribavirin. Efficacy varies depending on multiple factors especially viral genotype, but achieving sustained viral suppression in 50% of patients can be expected (see Figure 2).

Figure 2

Sustained virologic response rates with peginterferon alpha-2a (PegIFN) or interferon alpha - 2b (IFN) and ribavirin (RBV) according to genotype[2]

1. Patient Evaluation and Treatment

Recommendations

Treatment should be considered for all patients with detectable HCV RNA and an abnormal liver biopsy, regardless of the presence or absence of liver enzyme elevation.

Prior to making a decision regarding treatment, patients should be evaluated with HCV RNA, HCV genotype, liver enzymes (ALT), and liver biopsy, unless contraindicated.

The decision to initiate antiviral therapy should be made based upon the willingness of the patient to undergo therapy, ability to regularly attend appointments, and agreement to use contraception to prevent pregnancy.

The decision to initiate antiviral therapy should be made on an individualized basis that considers severity of liver disease, co-morbid conditions, the potential for serious side effects and the likelihood of response.

Patients with HCV infection on methadone maintenance therapy should not be considered ineligible for treatment.

The treatment of the actively using injection drug user is not contraindicated and may be appropriate under some circumstances.

Patients with a history of well-controlled psychiatric disorders may be excellent candidates for antiviral therapy and should be under the care of a qualified mental health professional.

Treatment of HIV/HCV co-infected patients should be offered with pegylated interferon and ribavirin, unless contraindicated.

Patients co-infected with HIV/HCV should be managed by experts in both viruses. The basic tenets of HCV management should not change, but the provider must be prepared for possible hepatotoxicity and drug-drug interactions. Further recommendations for the HIV/ HCV co-infected patient are provided at: www.hivguidelines.org/public_html/hep-c/adl-hepc.htm

All patients with CHC infection are candidates for antiviral therapy. These patients are defined by detectable serum HCV RNA and an abnormal liver biopsy consistent with chronic liver disease. Treatment is recommended for patients with significant inflammation or fibrosis. [23]

There are relatively few contraindications to antiviral therapy although the decision to initiate therapy should be made after ensuring that the patient understands the risks and benefits of pegylated interferon and ribavirin. Current absolute contraindications to combination therapy include a known hypersensitivity to pegylated interferon and/or ribavirin, autoimmune hepatitis, decompensated liver disease, pregnant women, men whose female partners are pregnant and patients with hemoglobinopathies.[56,57] Many patients with hepatitis C will also have underlying mental illness such as depression. Uncontrolled psychiatric illness and suicidal ideations or attempts are contraindications to antiviral therapy. Patients with remote histories of suicidal ideation or attempt warrant further evaluation to assess suitability for treatment. On the other hand, patients whose psychiatric disorders are under control and who are regularly followed by mental health providers are often excellent candidates for antiviral therapy.

IDU is the most common mode for acquisition of HCV infection. Patients with a history of injection drug use who are no longer using recreational injection drugs are treated in the guidelines as noted above. Methadone use has not been shown to adversely affect SVR rates or interfere with patient adherence to medication regimens. Patients enrolled in methadone maintenance programs should be considered for antiviral therapy. [58]

The treatment of actively injecting drug users is controversial and raises concerns related to adherence to therapy and the potential for re-infection. Patients actively using injection drugs should be offered drug counseling and psychiatric support services. Like all patients, treatment of the actively injecting drug using person should be based upon the willingness of the patient to undergo therapy, ability to regularly attend appointments for close monitoring, and agreement to use of contraception to prevent pregnancy.

2. Environmental Assessment and Support

Environmental support is an important part of patient assessment because treatment may be given for up to one year, and the adverse effects of treatment may incapacitate patients. A patient's living situation and household income should be addressed prior to treating treatment. Homelessness may be a significant problem, and the need for a support network for such patients should be assessed and arranged before the treatment. In addition, most formulations of pegylated interferon now require refrigeration. Family meetings can be helpful to prepare family members for side effects of treatment. Neuro-psychiatric side effects such as irritability and hostility can strain relationships if unexpected. These issues can be assessed with the collaboration of social services. Family and friends may need to help with activities of daily living including transportation to medical appointments. Home health nurses and case managers may be helpful in providing support at home.

3. Initiating Treatment

Recommendations

Prior to treatment, patients should have a baseline complete blood count (CBC), chemistry evaluations, serum creatinine, thyroid function tests, pregnancy tests in women, HIV testing, contraceptive counseling for men and women, and screening for depression.

Prior to initiating treatment, patients should be informed of the possible side effects of therapy to allow them to anticipate and manage with these side effects.

The treatment of choice for patients with chronic hepatitis C infection is combination pegylated interferon and ribavirin.

Patients infected with genotype 1 or 4 should be treated for 48 weeks with combination pegylated interferon and ribavirin. The ribavirin dose should be 1000 mg a day in patients ≤ 75 kg and 1200 mg a day in patients > 75 kg.

Patients infected with genotype 2 or 3 should be treated for 24 weeks with combination pegylated interferon and ribavirin. The ribavirin dose should be 800 mg a day.

Several treatments are licensed in the U.S. for the treatment of CHC. These agents include interferon alpha-2a, interferon alpha-2b, interferon alpha con-1, and interferon alpha-2b in combination with ribavirin; pegylated interferon- alpha 2b alone and in combination with ribavirin; and interferon alpha-2b and pegylated interferon alpha-2a alone and in combination with ribavirin. Data from multiple clinical trials clearly supports the use of pegylated interferon in combination with ribavirin.

Pegylated interferon has been a major advance in the treatment of CHC. The concept behind the pegylation of interferon is to produce a molecule which maintains longer lasting therapeutic concentrations by optimizing both absorption and distribution while decreasing the rate of clearance and deceasing proteolysis. This is accomplished by the addition of a polyethylene glycol molecule [PEG] to standard interferon by way of a covalent bond. This PEG molecule is non-toxic polymer that is readily excreted in the urine. The PEG molecule can be either linear or branched. Larger PEG molecules produce greater reductions in renal clearance and provide more subcutaneous absorption.

Two pegylated molecules are currently being used in the U.S. Pegylated interferon alfa-2b (Peg-Intron; Schering-Plough) is a linear 12 KD molecule, and pegylated interferon alfa-2a (Pegasys; Roche) is a 40KD branched chain molecule. These products are both manufactured using recombinant DNA technology in an Escherichia coli system. Both products have dose related maximum concentrations. Pegylated interferon alfa-2a is given as a fixed dose whereas pegylated interferon alfa-2b is dosed according to patient weight.

One study compared once weekly pegylated interferon alfa-2a with standard interferon alfa-2a three times a week for 48 weeks in previously untreated patients with hepatitis

C.[59] The SVR rate in the pegylated interferon group was 39% compared to a 19% response rate in the standard interferon group. The SVR rate of genotype 1 patients receiving peginterferon alfa-2a was 28%. The frequency and severity of adverse events was similar in both groups. Pre-treatment factors that were associated with a sustained virologic response in this study, in order of significance, include genotype other than type 1, ALT quotient greater than three, HCV RNA level less than two million copies (Cobas Amplicor HCV-PCR version 2; Roche), body surface area less than 2 meters^2, lack of bridging fibrosis or cirrhosis, and age less than 40 years. Side effects were less with the group treated with pegylated interferon alfa-2a than the group that received standard interferon therapy.

The highest SVR rates in previously untreated patients with chronic hepatitis C have been reported with combination pegylated interferon and ribavirin. In one study of 1530 patients, a 54% SVR was reported in patients treated with pegylated interferon alfa-2b plus ribavirin.[60] This was compared to a 47% SVR rate in patients treated with three times a week standard interferon plus ribavirin. The response rates to pegylated interferon alfa-2b plus ribavirin for genotypes 1 and non-1 were 42% and 82%, respectively.[2] In a retrospective analysis of the data, the authors report that patients receiving more than 10.6 mg/kg of ribavirin had higher sustained response rates, regardless of treatment group. Another study showed that patients with genotypes other than type 1, regardless of ribavirin dose and treatment duration, had a sustained reponse of 80%, leading to the recommendation that non-type 1 patients can use a ribavirin dose of only 800 mg and can discontinue treatment after 24 weeks.[61]

Side effects between the groups receiving pegylated interferon alfa-2b and standard interferon were similar although there was significantly more fever, weight loss, nausea and injection site reactions in the group receiving pegylated interferon alfa-2b.

Several studies have documented a decreased sustained viral response rates in African-American patients infected with hepatitis C

when compared to Caucasians and Asian-Americans. One prospective study evaluating the SVR rates of African-Americans and whites receiving pegylated interferon alfa-2a plus ribavirin for 48 weeks, reported a response of 26% for blacks compared to 39% for whites.[62]

4. Monitoring While on Treatment

Recommendations

Patients who do not achieve virologic suppression or a 2- log decrease in HCV RNA at 12 weeks may have therapy discontinued, although factors such as degree of fibrosis and tolerability of therapy should be considered.

Patients should have a CBC and chemistry evaluations 2 weeks after initiation of treatment to assess for potential toxicities.

CBC, chemistry evaluations, and pregnancy tests in women should be done routinely at each follow-up visit and not less often then every 4-6 weeks during treatment.

Patients who achieve an end-of-treatment virological response should have HCV RNA testing performed 24 weeks after stopping treatment to evaluate for a SVR.

Erythropoetin alfa and granulocyte colony stimulating factor (G-CSF) may be used to treat anemia and neutropenia, respectively, in order to maintain the patient on full medication doses.

Providers should reference the full discussion of side effects of hepatitis C treatment in Appendix A.

One analysis of pegylated interferon alfa-2b plus ribavirin showed that genotype 1 patients who did not achieve either viral eradication or a drop in baseline HCV RNA by more than 2 log at 12 weeks of therapy had <1% chance of achieving a SVR. Patients who do not achieve this "early viral response" can have therapy discontinued. This action is both cost effective and can improve patient quality of life. [63]

The key factor in achieving a sustained viral response with pegylated interferon and ribavirin appears to be the patient's ability to adhere to the treatment regimen. Adherence is directly related to side effects and tolerability. Better understanding of the toxicities and side effects of combination therapies and their management should lead to better outcomes.

Common side effects of pegylated interferon plus ribavirin therapy include the development of flu-like symptoms, fatigue, alopecia, rash, cough, insomnia, anorexia, thyroid disease, injection-site reactions, vision disorders, anemia, neutropenia, and thrombocytopenia. Rarely, colitis, pancreatitis, and severe pulmonary disease have been observed on alfa-interferon and ribavirin therapy.[56,57]

Ribavirin may cause birth defects and/or death to the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking pegylated interferon plus ribavirin. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of child-bearing potential and men must use two forms of effective contraception during treatment and for at least six months after treatment has concluded. Monthly pregnancy tests must be performed routinely throughout the treatment and follow-up phases.[64]

Pegylated interferon and ribavirin have been found to be safe and effective in HCV mono-infection and in co-infection with HIV.[2,61] Safety and efficacy has not been established in patients who have received liver or other organ transplants, in patients who have failed other alpha interferon treatments and in patients under the age of 18.[56,57]

Neutropenia is commonly seen with pegylated interferon alfa-2b, and 18% of those receiving pegylated interferon at 1.5 ug/kg required a dose reduction due to significant neutropenia. Anemia secondary to ribavirin was also common. Ribavirin dose reduction was seen in 9% of patients treated with pegylated interferon 1.5 ug/kg in combination with 800 mg of ribavirin, and in 13% of those treated with standard interferon and 1000-1200 mg of ribavirin.

5. Re-treatment of Patients Previously Treated for Hepatitis C

Recommendations

Re-treatment of inadequately treated patients is recommended with a combination of pegylated interferon and ribavirin.

Re-treatment of non-responders or relapsers to antiviral therapies other than a combination of pegylated interferon and ribavirin should be strongly considered.

Re-treatment of Patients Who Failed to Respond to Previous Therapies

A large segment of patients with hepatitis C fall into the category of those who did not respond previous to therapy. A careful history must be obtained in these patients to determine if re-treatment should be considered. Patients who did not respond to therapy fall into three general categories: (1) those who were inadequately or inappropriately treated initially, (2) non-responders and (3) relapsers. In addition, patients may fit into any of these three categories after treatments with interferon monotherapy, three-times-weekly interferon plus ribavirin, or pegylated interferon plus ribavirin.

Re-treatment of Inadequately or Inappropriately Treated Patients

Inadequately treated patients are those who either received less than the recommended doses of interferon or ribavirin or were treated for a shorter duration of therapy to make an appropriate assessment as to their response. It is important that all treated patients are encouraged to remain on the baseline dosages of interferon or ribavirin unless untoward effects necessitate dose reduction for a minimum of 12 weeks in order for an assessment of early viral response to be obtained. Inadequately treated patients should be considered for re-treatment with pegylated interferon and ribavirin if no contraindications are noted.

Re-treatment of Non-responders

In patients previously treated with interferon monotherapy, approximately 25-40% may achieve a SVR when treated with pegylated interferon and ribavirin. [66,67] Approximately 10% of patients who did not respond to three-times-weekly interferon plus ribavirin will have a SVR with pegylated interferon and ribavirin. Factors associated with a response to retreatment include non-genotype 1 infection, lower baseline HCV RNA levels, less fibrosis on liver biopsy and non-African-American race.[66,67] There currently are no published data on the re-treatment of patients who fail to respond to treatment with pegylated interferon and ribavirin.

Re-treatment of Relapsers

Relapse is defined as the reappearance of serum HCV RNA in a patient with previously undetectable HCV RNA at the end of antiviral therapy. Relapse following interferon monotherapy is more common than relapse following combination interferon and ribavirin therapy or combination pegylated interferon and ribavirin therapy.

Large studies show that often relapsers following monotherapy with interferon alone respond favorably to standard interferon plus ribavirin. It seems reasonable to presume that such relapsers will respond to combination pegylated interferon plus ribavirin.

The growing problem facing physicians today is how to approach the patient who relapses following combination interferon plus ribavirin or combination pegylated interferon plus ribavirin therapy. Unfortunately, there are limited data currently available to address this issue.

6. Treatment of HCV-Infected Children

Recommendations

Diagnostic evaluation for the presence and severity of HCV infection, including liver biopsy, should be performed in children as in adults.

Therapy with standard interferon and ribavirin may be offered to children aged 3-17

years if given under the care of experienced physicians.

Antiviral therapy should not be administered to children under the age of three.

Children infected with HCV are less likely to manifest symptoms and are more likely to have normal or minimally abnormal liver tests compared with adults. They generally have a slower rate of progression to advanced liver disease. However, there are multiple factors that support treatment of HCV infection in children. These factors include the anticipated long duration of infection after early acquisition, relatively good tolerance of antiviral medications, and avoidance of social stigmatization. Nevertheless, careful selection of appropriate candidates for therapy is important. If a contraindication to current therapeutic agents is present, treatment should be withheld until this has resolved or until new agents are available. Children without contraindications to the medications used for hepatitis C should undergo liver biopsy to determine the presence and degree of fibrosis. In the absence of fibrosis, treatment may be deferred. If any degree of hepatic fibrosis is present, antiviral therapy for HCV should be considered. At present, in the U.S., the only therapy approved for children by the FDA is a combination of interferon alfa-2b and ribavirin. The results of several studies using interferon monotherapy or combination therapy with standard interferon and ribavirin indicate that SVR rates are as good or better than those achieved in adults. Children generally tolerate interferon therapy better than adults; in small numbers of children reported so far dose-dependent hemolytic anemia has been less severe than in adults.[68] Although safety data have not yet been developed, pegylated interferon in combination with ribavirin offers improved efficacy and should be considered in adolescents older than 16 years of age who are post-pubertal, or in younger children in the context of clinical trials. Multicenter trials are currently underway to determine the safety and effectiveness of other forms of therapy for HCV infection in children.[68] The safety and pharmacokinetics of hepatitis C therapies have not been determined for children younger than 3 years of age.

7. Treatment of Individuals with Acute Hepatitis C Infection

Recommendations

Although there are no controlled trials recommending treatment of acute HCV infection, the use of pegylated interferon monotherapy may prevent the development of CHC infection, although the duration of therapy in still unknown.

There are insufficient data to recommend the use of ribavirin in the acute setting.

Therapy should be deferred until 12 weeks after exposure, to allow for spontaneous clearance to occur, thus avoiding therapy.

The acute phase of HCV infection is seen as a window of opportunity during which the establishment of chronic hepatitis C and its associated morbidity may be prevented.[22] A meta-analysis of trials of various interferon alfa monotherapy regimens showed an average SVR rate of 42%, although the quality of these trials was variable. [69]

Acute HCV infection is seldom seen in clinical practice. Therefore, there is a paucity of well-designed, randomized controlled trials for the treatment of this patient.[70] One study reported that intensive treatment of acute hepatitis C with interferon alfa-2b resulted in a 98% SVR. Although there is no standard therapy for the treatment of acute hepatitis C, this study strongly suggests that treatment with interferon monotherapy at higher than standard doses is highly effective in eradicating acute infection.[71] Two more recent studies have reported on the effectiveness of pegylated interferon monotherapy for acute hepatitis C.[72,73] These studies support initiating therapy after an initial waiting period of approximately 12 weeks after exposure to allow for spontaneous clearance to occur, thus avoiding therapy altogether.

F. Medical Management

Recommendations

A multidisciplinary team approach is recommended for HCV patients with active co-occurring alcohol, substance abuse disorders and/or psychiatric illnesses who are not ready for antiviral treatment.

Patients with Unstable Drug Use

Perform a comprehensive substance abuse assessment, including type(s) of substance(s), frequency, quantity, method of use, environment, and change in use over time. Identify whether injection drug users share syringes, cookers, cotton, or water; and where the equipment is obtained.

Assess patient's understanding of his/her substance abuse disorder, readiness for change, and willingness to engage in substance abuse treatment.

Educate patient on the requirements for initiating antiviral treatment. In particular, clarify that drug abstinence is not a requirement for antiviral treatment. Conversely, alcohol abstinence is recommended for patients with alcohol abuse and/or dependence as heavy alcohol use adversely affects treatment outcomes.

Encourage patient to seek substance abuse treatment or harm reduction program (i.e. syringe exchange program). Make appropriate referrals for patients interested in pursuing treatment, counseling, and/or supportive services. Collaborate with addiction specialist to reassess for antiviral treatment eligibility.

Assess stability of substance use and eligibility for antiviral treatment at periodic intervals.

Patients with Unstable Alcohol Use

Patients with HCV infection who use alcohol need to be educated regarding the effects of alcohol on the course of HCV infection.

Patients with alcohol abuse or dependence should be referred for chemical dependency treatment.

Patients with alcohol abuse or dependence should be encouraged to enroll in a rehabilitation program and establish abstinence prior to treatment.

Patients who consume light or moderate amounts of alcohol should be advised to abstain from alcohol during antiviral therapy, but a pretreatment period of abstinence is not necessary.

Patients with Unstable Psychiatric Illness

Refer patients to a mental health provider for treatment and stabilization. Collaborate with mental health provider to reassess for antiviral treatment eligibility.

Assessment for antiviral treatment readiness should include an assessment of the patient's supportive networks, both formal and informal. Family meetings may help clarify expectations for the initiation of antiviral treatment, and promote family support to the patient.

Patients with unstable psychiatric illness who refuse to engage in psychiatric treatment are not candidates for antiviral treatment.

Assess stability of psychiatric illness and eligibility for antiviral treatment at periodic intervals.

Patients not currently undergoing antiviral therapy should be reassessed periodically for eligibility and interest. Providers and patients should actively address substance abuse, psychiatric, and medical co-morbidities in order to prepare for antiviral treatment.

All patients may benefit from hepatitis C support groups and peer education, whether or not they are undergoing antiviral treatment.

The 2002 National Institutes of Health (NIH) Consensus Statement and the 2004 AASLD Practice Guidelines recognized that patients with co-occurring alcohol, substance use, and psychiatric illness may be effectively treated for HCV infection.[22,23] Indeed, a growing number of studies provide preliminary support for the use of interferon-based therapy for

patients with HCV infection who have active substance use disorders and psychiatric illnesses. In order for this to be successful, a multidisciplinary approach should be used.[74] Multidisciplinary models may include providers skilled in HCV, HIV, psychiatric and addiction medicine, as well nurses, social workers, substance abuse counselors, and case managers. A multidisciplinary approach promotes stabilization of psychiatric illness and monitoring of addiction prior to and during antiviral treatment. This approach also allows for a better overall coordination of patient care through the sharing of pertinent medical information needed to ensure patients and providers are fully informed about the treatment plan, any drug interactions, and that the patient receives consistent counseling messages.

Although coordination of care among primary care, psychiatric, and addiction service providers may best serve HCV-infected patients with co-morbidities, many medical care systems are not currently equipped to provide this comprehensive multidisciplinary service. A multidisciplinary approach is also possible through off-site linkages. Additionally, healthcare providers should seek additional training in order to develop expertise in addiction, psychiatry and HCV-related care.

1. Management of Patients with Unstable Drug Use

Although the above guidelines endorse the treatment of HCV infected patients with active drug use and patients with psychiatric illnesses on an individualized basis, there are some patients with unstable substance use disorders and/or psychiatric illness in whom immediate antiviral therapy is not warranted. Decisions regarding stability of addiction and psychiatric illness should be made in collaboration with an addiction specialist and psychiatrist whenever feasible. For these unstable patients, the focus should be on stabilization of addiction and/or psychiatric illness.

It is important to note that decisions made about eligibility of active drug users for antiviral treatment should be individualized and not be based primarily on type of drug, route of use, quantity, and/or frequency, but rather on safety of drug use, stability of psychiatric illnesses, and ability to adhere to appointments and treatment.

Patterns of drug use that may indicate that antiviral treatment should be delayed include:

- Drug seeking, drug use, and recovery from drug use that sufficiently disrupts the daily routine so that it prevents regular adherence with appointments and antiviral medications.

- Drug use which impairs patient's ability to engage appropriately with the physician.

It has been shown that linking all of a substance user's needs is beneficial for both the active user and the various providers involved in his/her care.[75] The medical management of HCV infection in complex patients may necessitate integration of interferon-based treatment into healthcare settings that care for substance using and psychiatrically ill patients. Such settings may include methadone clinics, prisons, mental health clinics, psychiatric hospitals, and enhanced walk-in clinics.[58] Successful on-site primary medical services have been developed in some drug treatment programs in response to the HIV epidemic, and there is preliminary evidence that on-site HCV care may be feasible in drug treatment programs as well.[76,77]

Providers should have a basic understanding of substance use treatments that are available and the activities that can be expected in each setting. This information can help providers better understand what patients may experience and better assist patients in choosing treatment settings that fit with their needs.[78] In addition, providers should explore whether or not the patient believes that the drug use is a problem, and if so what his/her goals are. Some may have a goal of abstinence whereas others may wish for decreased drug use, or safer drug use.

Options for treatment include pharmacotherapy for opioid addiction with opioid replacement therapies such as

methadone or buprenorphine. Detoxifications (alcohol, heroin, or benzodiazepine) and short-term inpatient rehabilitation programs may also be useful when coupled with a comprehensive aftercare plan. Long-term residential treatment may be appropriate for persons who are interested but unable to achieve abstinence in the community setting. Patients should be informed of twelve-step programs such as Alcoholics Anonymous (AA) and Narcotics Anonymous (NA), but there is insufficient evidence to insist that patients take part in them if they are not self-motivated to do so.

Harm reduction is central to drug treatment, and is an approach that puts the well being of the user and society above the goal of abstinence. Harm reduction recognizes that while abstinence is one means of reducing drug-related harm, a drug user's major concern may not be cessation of drug use. Some keys to harm reduction in opioid addiction are syringe access, overdose prevention, and vaccination. Education is the backbone of harm reduction. When drug users are educated about the risks involved in drug use and are offered tools to reduce these risks, many alter their behavior. The provider should discuss how the patient obtains the injection equipment (syringe exchange program, expanded access pharmacy program, etc.), and the patient should agree to discuss ongoing drug use and high-risk behaviors.[78]

Drug users motivated to receive antiviral treatment are encouraged to abstain from the use of drugs and enroll in a substance abuse treatment program or harm reduction program. Individuals are not required to achieve abstinence prior to initiation of antiviral therapy, but ideally receive antiviral treatment and substance abuse treatment services concurrently.[79] The clinician should make clear what the expectations are for initiating antiviral treatment. A clinician should reassess for stability of drug use and eligibility for antiviral treatment at periodic intervals.

2. Management of Patients with Alcohol Use

Numerous studies indicate that patients infected with HCV and heavy alcohol intake have increased progression of hepatic fibrosis and increased risks of cirrhosis, hepatocellular carcinoma, and death.[80,81] While some studies suggest that light to moderate consumption may contribute to progression, this has not been clearly shown.[82]

All patients with HCV infection who use alcohol need to be educated regarding the effects of alcohol on the course of HCV infection. Abstinence in heavy drinkers infected with HCV is associated with improvement in chemical markers as well as a decrease in HCV RNA levels.[83,84] Patients with alcohol abuse or dependence should be referred for chemical dependency treatment.

There are limited data on patients with ongoing alcohol use during antiviral treatment. One study found a inverse correlation between rates of response to interferon treatment and levels of alcohol intake during therapy.[85] Furthermore, there are reports of acute alcoholic hepatitis in several individuals consuming alcohol during interferon treatment.[86] Individuals with alcohol abuse or dependence should be encouraged to enroll in a rehabilitation program and establish abstinence prior to treatment. Patients who consume light or moderate amounts of alcohol should be advised to abstain from alcohol during antiviral therapy, but a pretreatment period of abstinence is not necessary.[79]

3. Management of Patients with Unstable Psychiatric Illness

Patients who are not currently eligible for antiviral treatment due to unstable psychiatric co-morbidities should be referred to a mental health provider who has an awareness of HCV treatment risks and who can collaborate during the period of antiviral treatment. Mental health providers are uniquely positioned to assist patients to undergo HCV evaluations and procedures, adhere to difficult treatment regimens, and monitor and treat neuro-psychiatric adverse events.[87] Ideally, patients should have 3 to 6 months

of symptom reduction to a socially stable level for anxiety, depression, and psychotic symptoms.[88] However, the decision regarding when to initiate treatment must be made on an individualized basis without arbitrary time limits.

4. Role of Support Groups and Peer Educators

The documented successes of support groups and peers educators in HIV-infected individuals may inform the development of similar programs for HCV-infected individuals. Participation in a HIV support group has been shown to have a positive impact on depression, anxiety, high-risk behavior, plasma viral load, CD4 cell count, and survival in HIV-infected individuals.[88-90] Similarly, peer education and role-modeling of positive behaviors in HIV-infected individuals have been proven to improve knowledge, attitudes, and behaviors; decrease psychological distress; increase quality of life; increase service utilization in target populations; and promote sustained behavior change.[91-95]

HCV support groups can focus on the basic steps of treatment, allow group members to share their experiences with evaluation and treatment, and engage in advocacy projects which promote sense of community.[77,96] The role of peer educators in promoting HCV evaluation and treatment should be further investigated.

In conclusion, the possibility of a cure from CHC may provide motivation for some patients to focus on the treatment of their other chronic diseases. Providers and patients must actively address substance abuse, psychiatric, and medical co-morbidities in order to prepare for antiviral treatment. These efforts may include becoming engaged in substance abuse care, adherence with psychiatric appointments and psychotropic medication, and renewed commitment to the long-term treatment of conditions such as diabetes, hypertension, and HIV disease. A treatment contract may be useful in order to set goals and expectations prior to antiviral treatment initiation.

5. Frequency of Viral Load Testing

Recommendation

Serial HCV viral loads should not be routinely performed for patients who are not receiving antiviral treatment.

If there has been a significant lapse in time between the initial quantification of viral load and the initiation of antiviral treatment, the clinician may reassess the viral load again to establish an accurate baseline. If there is a history of excessive alcohol intake, the clinician may reassess the viral load prior to initiation antiviral treatment, as alcohol is known to increase viral load.[97,98]

6. Frequency of Liver Biopsy

Recommendation

Liver biopsies every 4-5 years may be considered for those patients in whom treatment is deferred because of mild fibrosis (Metavir score <2 or Ishak score <3) if progression of disease affects the decision to treat. [22]

Although there is no strong evidence to support more frequent biopsies, the clinician may choose to repeat liver biopsy sooner in patients with HIV/HCV co-infection. In patients with HIV/HCV co-infection, liver disease advances more rapidly, and there is a two-fold higher risk of cirrhosis.[99]

7. Management of Patients with Decompensated Liver Disease

Recommendation

An HCV-infected patient with decompensated liver disease should always be managed by, or in conjunction with, an expert in liver diseases.

Inflammation, necrosis and fibrosis due to chronic, active infection with HCV can lead to cirrhosis and decompensated liver disease. Decompensated liver disease in patients with cirrhosis is defined as the development of at least one of the following conditions: variceal hemorrhage, encephalopathy, reduced hepatic synthetic function (low serum albumin, elevated INR), or ascites.[22] Up to 20% of HCV-infected patients will develop cirrhosis after 20

to 30 years, of whom one-third will progress to decompensated liver disease and 1% to 2% will develop hepatocellular carcinoma.[22,23,100] Risk factors for progression to cirrhosis include: older age, obesity (and associated hepatic steatosis), male gender, HIV co-infection, and alcohol consumption (>50 grams/day).[101-103] End stage liver disease due to CHC infection is the most common reason for liver transplantation in the U.S.

8. Timing of Referral for Liver Transplant in Patients with HCV-associated Cirrhosis

Recommendations

All attempts should be made to treat HCV infection pre-transplant even in patients with decompensated liver disease.

Any patient with decompensated liver should be evaluated by a liver transplant specialist.

Indications for referral for liver transplant are based on the development of conditions that are known to shorten survival (anticipated survival of less than one year), thereby justifying the risk of the procedure. Referral should be made as soon as the patient has developed decompensated liver disease due to the long projected waiting time for transplantation. Patients should be referred to a liver transplant center for the following reasons:[104]

- Development of ascites (especially ascites that is refractory to medical therapy).

- Spontaneous bacterial peritonitis.

- Hepatorenal syndrome defined as renal failure due to vasoconstriction of renal vasculature and renal hypoperfusion (Acute [Type 1], and stable/slowly progressive [Type 2]).[105]

- Hepatic encephalopathy.

Contraindications for liver transplant include uncured extrahepatic malignancy and other severe uncontrolled medical illness (e.g., end-stage cardiomyopathy or advanced chronic obstructive pulmonary disease). Although a period of abstinence from alcohol and

active substance abuse is required by many centers, methadone patients have been found to be good candidates for transplant.[106] HIV infection before the availability of highly active antiretroviral therapy (HAART) was often considered a contraindication for liver transplant, improved survival with HAART therapy has enabled consideration of patients.[107,108]

Once referred for liver transplant, patients are prioritized for surgery based on policies determined by the United Network for Organ Sharing (UNOS) according to their Model for End-Stage Liver Disease (MELD) score. Patients with fulminant liver failure with very short life expectancy receive the highest priority, but due to the constriction of time and the scarcity of donor organs many of these patients do not find a suitable donor. Priority for transplantation is based on the MELD score for prediction of short-term (3-6 month) mortality, defined as: [109]

- $3.8 \log (\text{bilirubin [mg/dl]}) + 11.2 \log_{10}(\text{INR}) + 9.6 \log_{10}(\text{creatinine [mg/dl]}) + 6.4(\text{etiology})$;

- Etiology = 0 if disease is due to cholestasis or alcohol;

- 1 for all other causes (including HCV).

Clinicians who manage patients with chronic liver disease may use the relatively easy-to-calculate Child-Turcotte-Pugh score to prognosticate and assess clinical/biochemical severity in conjunction with other relevant clinical information (see Table 3). Note, that the Child-Turcotte-Pugh score is not used as an assessment tool for liver transplantation.

Virtually all patients with HCV who undergo liver transplantation will develop recurrence of HCV infection, often with a more rapid progression of disease in the transplanted organ.[108,110] Therefore, all attempts should be made to treat HCV infection pre-transplant even in patients with decompensated liver disease.[22] The risks and benefits of HCV treatment must be weighed carefully for the patient with decompensated liver disease due to the potential for lower response rates and higher toxicity including: leukopenia, anemia, thrombocytopenia, increased infection risk and

Table 3

Child-Turcotte-Pugh Scoring System for Severity of HCV

Feature	Points		
	1	2	3
Encephalopathy*	Stage 0	Stage 1-2	Stage 3-4
Ascites	Absent	Mild-Moderate	Severe
Serum Bilirubin (mg/dL)	< 2	2-3	>3
Serum Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
INR	<1.3	1.3-1.5	>1.5

Score: Class A = 0-6 points; Class B = 7-9 points; Class C = 10 or more points

*Mental status in hepatic encephalopathy can be graded by use of the West Haven criteria

- Stage 0: Normal behavior and personality; no asterixis.
- Stage 1: Mild decrease in orientation, attention deficit, impaired ability to calculate (addition/subtraction), abnormal sleep pattern (hypersomnia, insomnia), mood alteration (euphoria or depression), irritability; with/without asterixis.
- Stage 2: Lethargy, drowsiness, inattentiveness, disorientation, memory deficit, dysarthria; asterixis is present.
- Stage 3: Severe disorientation, obtundation (but arousable), inappropriate behavior, stupor, clonus; asterixis not usually present.
- Stage 4: Coma, dilated pupils.

possible acceleration of liver decompensation. Treatment of patients with end-stage liver disease from HCV infection should entail close monitoring for treatment related toxicity and judicious use of colony-stimulating growth factors and dosage modifications. [22]

9. Liver Health

Hepatotoxic Drugs

Recommendations

Providers should discuss the role played by alcohol in the progression of hepatitis C.

Providers should warn patients to be aware that over-the-counter medications can be hepatotoxic and that they should discuss medication use with a medical provider.

Patients should be made aware that no herbal products have yet been shown to delay progression of hepatitis C and that some herbs are hepatotoxic.

Heavy alcohol use (greater than or equal to 50 grams per day) is strongly associated with progression of hepatitis C. The effects of light to moderate use are not as well studied but have not been clearly associated with increased fibrosis.[82] The National Institute on Alcohol Abuse and Alcoholism states that safe levels of alcohol use for healthy people are up to 2 drinks/day for men and 1 drink per day for women and for persons over 65. One drink consists of 12 ounces of beer, 5 oz of wine or 1.5 ounces of liquor and contains 14 grams of alcohol. While heavy alcohol use is contraindicated in HCV patients, it is not clear that all patients must eliminate moderate use of alcohol.

Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, have been have been associated with hepatitis C flares. There are no reports of adverse effects of acetaminophen when taken as directed and without alcohol. [111] Many patients take herbal preparations for a variety of illnesses, including hepatitis C. The National Center for Complementary and Alternative Medicine has funded several clinical trials studying the effects of herbal preparations on hepatitis C progression including one of a widely used herb, silimarin, or milk thistle. [112]

Injection Drug Users

Recommendations

Injection drug users should be advised to stop injecting, and seek treatment if indicated.

If unable to stop, IDUs should be advised to obtain sterile syringes from pharmacies or syringe exchanges and to avoid sharing any injection equipment.

Risk Reduction and Partner Notification

Recommendations

Non-monogamous patients should use condoms and other barrier methods with sexual partners.

HCV- positive patients should be advised to avoid sharing items that may be contaminated with blood such as toothbrushes and razors; blood spills should be promptly cleaned.

Providers should be available to assist patients when they inform partners and family members about their HCV status to provide information on transmission, treatment and prognosis.

Numerous long-term studies find minimal risk of transmission among monogamous heterosexual couples; therefore, the CDC does not recommend condoms under this circumstances.[113] However, some couples may choose to use them. There are no data regarding monogamous same sex partners but HCV is not substantially higher among homosexual men. There have been case reports of nonsexual household transmission, however such transmission is rare and routine testing of household members is not recommended.[19]

While HCV infection is a reportable disease, there are no regulations or guidelines regarding partner notification of people with HCV infection. However, patients with HCV infection are encouraged to notify their at-risk partners. Two useful public health strategies for notification are: (1) the patient may chose to notify sex and needle-sharing partners, or (2) the physician may notify partners with the patient's permission.

G. Hepatitis C Post-exposure Management

Recommendations

At time of exposure:

Determine the type of exposure and assess the associated risk.

Wash wounds with soap and water; flush mucous membranes with water.

No post-exposure prophylaxis (immune globulin or antiviral medications) is recommended.

Counsel the exposed person regarding hepatitis C transmission risk.

Test source and exposed individual for hepatitis C virus antibody (figure 1) and liver enzymes for exposed individual. If source is not available or refuses testing, treat exposed person as if source has active hepatitis C infection.

If source is hepatitis C virus antibody positive, or is antibody negative and is immunocompromised, test source for qualitative HCV RNA.

If source is negative for hepatitis C antibody (and HCV RNA, if indicated), no further testing is necessary and no further action beyond initial HCV testing, is necessary for the exposed person.

If source is positive for hepatitis C antibody and HCV RNA , and exposed person is negative, follow up of exposed person should be done (see Figure 3).

The risk of transmission of HCV after a needlestick exposure from a hepatitis C-positive source is estimated at between 2-10% .[114-116] This is less than the risk of hepatitis B virus transmission from a hepatitis B-positive source, but higher than the risk of HIV transmission from an HIV-positive source.[117] The risk of transmission from a needlestick exposure depends upon the concentration of HCV RNA in the blood of the source patient and the volume of the inoculum. The risk of transmission of HCV from a single mucous membrane exposure is very rare. Although post-exposure prophylaxis with immune globulin was used in the past, it was ineffective and currently no post-exposure prophylaxis is recommended. The current recommendations for post-exposure monitoring

and management of bloodborne exposure to HCV are based on the natural history of acute hepatitis C disease and the available treatment regimens.

1. Recommendations for Post-exposure Management

The recommendations for management of bloodborne exposure to HCV are summarized below and a management algorithm is provided in Figure 3. Immediate management after needlestick or other bloodborne exposure includes cleansing of wounds and mucous membranes, determination of the nature of exposure, and post-exposure counseling as to the transmissibility of HCV and the implications of transmission. Since post-exposure prophylaxis with immune globulin is ineffective and since antiviral therapy that is delayed until after the onset of viremia may be highly effective, no immediate post-exposure therapy is recommended. Initially, both the source and exposed persons need to be tested for hepatitis C antibody. In addition, liver enzyme testing should be performed on the exposed person. If the source patient is anti-HCV negative, no further testing is needed. However, since some immunosuppressed patients are negative for hepatitis C antibody despite viremia, qualitative HCV RNA testing also may be needed at this stage. If the source or exposed person is positive for hepatitis C antibody, follow-up with qualitative HCV RNA testing is needed to determine active HCV infection. If the source and exposed persons are anti-HCV and HCV RNA positive on initial testing, they should be counseled and managed as in chronic hepatitis C. [22]
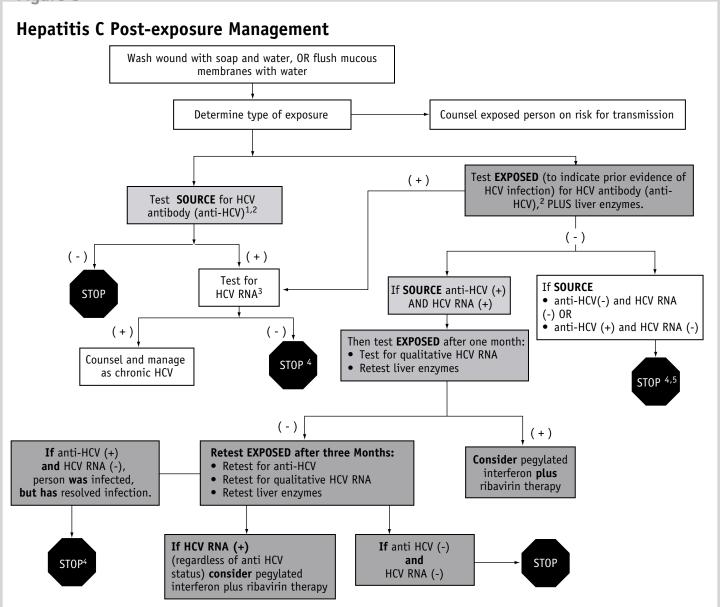
If the exposed person is anti-HCV negative initially, one month after exposure, the exposed person should be tested for qualitative HCV RNA and have liver enzymes repeated. If the exposed person is newly HCV RNA positive at this point, he/she may be offered antiviral therapy. However, because of the high rate of spontaneous clearance of infection between 6-12 weeks after transmission, it is recommended to defer therapy until the results of HCV RNA testing at twelve weeks

are available. Since patients with symptoms of acute hepatitis C have a higher rate of spontaneous viral clearance, it is more strongly recommended to defer therapy in these patients.

If three months after the exposure, the exposed person remains anti-HCV negative, repeat testing for anti-HCV, qualitative HCV RNA, and liver enzymes. Exposed patients who are PCR positive at this point should be offered

antiviral therapy unless contraindicated. Pegylated interferon therapy should be offered because of ease of administration and preliminary evidence of efficacy in acute hepatitis. [72,73] Ribavirin may be given as well if there are no contraindications, although the data on combination therapy in acute hepatitis C is even more limited. Monitoring and treatment regimens approved for the therapy of CHC should be used.[22]

Hepatitis C Post-exposure Management

[1] If source is unavailable or refuses testing, treat exposed as if source was anti-HCV (+) and HCV RNA (+).
[2] Since immunosuppressed persons can be negative for hepatitis C antibody despite viremia, qualitative HCV RNA testing should be performed.
[3] Qualitative HCV RNA by PCR or TMA.
[4] Person was HCV-infected at one time and spontaneously cleared the virus. Person is NOT able to transmit HCV at that time.
[5] Advise and counsel EXPOSED person if SOURCE person is anti-HCV (+) only.

H. Prevention and Counseling

Recommendations

The medical team should have an understanding of the significance and importance of the available HCV tests.

Prior to ordering testing, assess the patient's ability, regardless of age, to comprehend the nature and consequences of HCV antibody testing. Defer testing if the patient's ability to understand is temporarily impaired.

Hepatitis C counseling, before and after HCV testing, (see Table 4) should be carried out to provide health education and to strengthen the therapeutic alliance between the medical provider and the patient. Signed consent is not required for HCV testing. However, when testing for HCV, HIV testing should also be recommended, if not done previously or to update a previous HIV test. HIV testing will require signed consent in these situations.

After the initial counseling visit is completed, document in the medical record that the counseling was done. Once the HCV test results are available and counseling based on the test results is completed, document in the medical record that counseling was done, the test results, and what the patient was told. Document any recommendations for partner/ spousal notification, referrals to other providers or agencies, and the plan for follow up/ treatment plan. For patients with positive tests, consider a second counseling visit.

Table 4

Elements of Hepatitis C Counseling Counseling Prior to HCV Testing

Initial counseling should review the following elements:

- Patient's prior history of HCV testing and counseling;
- Incidence and prevalence of HCV;
- HCV transmission;
- Relationship to other diseases such as substance dependence, HIV, sexually transmitted diseases;
- Benefits of early diagnosis and intervention– prevention of transmission to others, reduced risk of long terms complications of HCV infection; and
- Treatment options.

The second part of hepatitis C counseling prior to testing is the explanation of specific test issues:

- Testing is voluntary;
- Tests and procedures, purpose of the test and that blood specimens are needed to perform the test;
- Explain the meaning of possible test results;
- When results should be expected and that results are occasionally delayed, which does not necessarily indicate a positive test; and
- Explain the confidential nature of clinician/ patient relationship.

The final part of hepatitis C counseling prior to testing includes:

- An explanation of risk reduction behaviors associated with HCV and other bloodborne diseases;
- A discussion of possible test results and that there will be post- test counseling; and
- Reassurance and/or referral for emotional support for the patient during the waiting period.

Counseling after HCV Testing*

For the patient with a negative test result:

- Discuss the meaning of the test result;

- Discuss possibility of HCV exposure during the past three months and the need for repeat testing if risk factors are significant;

- Emphasize that a negative test result does not imply immunity to future infection;

- Reinforce that the patient should not:

  - share needles;

  - ink or needles for tattoos;

  - needles for body piercing;

  - razors, toothbrushes or other personal items that could have blood or secretions on them; and

- Reinforce personal risk reduction strategies such as using latex condoms.

For the patient with a positive HCV antibody test result, discuss:

- Meaning of the test result (antibody test vs. viral load test);

- Possible risk factors that were present in the history; and

- Follow-up testing with a qualitative HCV RNA.

For the patient with a positive HCV antibody test result and a negative qualitative HCV RNA, discuss:

- Need for repeat qualitative HCV RNA in several months, if there are significant risk factors present, as the viral load can fluctuate;

- That a positive antibody and two negative qualitative HCV RNA tests at least 6 months apart means that the patient cannot transmit hepatitis C;

- That a positive antibody test does not confer immunity from future hepatitis C infections and that risk reduction is still important; and

- The possibility of acute infection that may have resolved spontaneously.

For the patient with a positive qualitative HCV RNA:

- Discuss that all new medications, including herbal medications and over-the-counter medications, need to be discussed with their physician prior to their use, as they could have deleterious effects on the liver;

- Inform the patient to minimize transmission to others, that he/she should not donate blood, body organs, tissue or semen, share anything that could have blood on it such as toothbrushes, razors, dental appliances, nail clippers, etc.;

- Cover all open sores to prevent spreading of possible infectious secretions;

- Discuss the harmful effects of alcohol use and HCV disease;

- Encourage partner/spousal notification with the options of self-notification or clinician-assisted notification;

- Encourage referral of needle sharing partners for HCV testing;

- Encourage referral of children of chronically infected women for HCV testing;

- For pregnant women infected only with HCV:

  - Breast-feeding should not be discouraged unless there are bleeding or cracked nipples and

  - When the mother is infected only with HCV, the vertical transmission rate is approximately 5% (range 3-7%);

- If the person has a long-term steady sexual partner the risk of transmission to the uninfected partner is low, though not absent. Barrier protection should be emphasized;

- Provide counseling or refer to counseling for coping with the emotional consequences of testing positive and behavior changes that will be needed to prevent the spread of HCV;

- Discuss availability of specialized medical care;

- Encourage vaccination for hepatitis A and B if the patient is susceptible;

- Provide or refer to HCV medical care for treatment; and

- Provide or refer the patient, family or significant others to support groups for counseling as needed.

*Refer to Hepatitis C Screening Algorithm (Figure 1) for HCV test interpretations

I. Summary

The advent of safe and effective antiviral therapy for hepatitis C and diagnostic technologies has shifted the treatment paradigm from liver transplantation for end-stage disease to ambulatory care. The public health infrastructure is in place to monitor trends in disease through HCV reporting and public health follow-up as needed. Primary care providers can assume an important leadership role in hepatitis C management and should be prepared to initiate HCV testing and provide counseling and information to patients. As part of a multidisciplinary team of hepatologists, social services providers, counselors, addiction medicine specialists and others, the primary care setting will often be the first point of contact for many newly diagnosed patients.

Side Effects of Treatment

Flu-Like Symptoms

Flu-like symptoms commonly develop on combination therapy. These symptoms include, but are not limited to, fever, chills, muscle aches, joint pains, headache, and fatigue. These symptoms usually occur within 2-24 hours of injection of pegylated interferon and tend to lessen in severity during the course of treatment. Injection of pegylated interferon at bedtime may lessen the severity of these side effects. Well-balanced meals and exercise may help the fatigue associated with therapy. As combination therapy can lead to mild dehydration, the importance of maintaining adequate hydration cannot be overemphasized. One twelve ounce glass of water every 3-4 hours can be very effective in treating the flu-like symptoms which may occur. Avoiding loud noises, bright lights, alcohol, caffeine and foods with tyramine and phenylalanine may also help to treat headaches. The headache, joint pains and muscle aches associated with therapy can be improved with the use of acetaminophen or non-steroidal anti-inflammatory medications such as ibuprofen. Regular-strength acetaminophen (325 mg tablets) use should not exceed six tablets a day and extra-strength (500 mg tablets) use should not exceed four a day. If headaches persist, despite these interventions, a physician should be consulted to look for other potential causes or treatment.

Gastrointestinal Side Effects

Nausea, anorexia and diarrhea may also complicate therapy. Ribavirin can cause nausea if taken on an empty stomach so it is important to take ribavirin with food. Smaller, more frequent meals will help to maintain adequate nutritional intake. Fatty foods should be avoided as these foods may worsen nausea. If nausea persists, anti-nausea medications such as ondansetron or prochlorperazine can be used.

Diarrhea should be initially evaluated by a physician to determine whether or not the medications are felt to be responsible. If diarrhea is due to interferon therapy, increased hydration, the use of anti-diarrheals and the institution of the BRAT (bananas, rice, apple sauce and toast) diet may improve symptoms. Significant weight loss secondary to nausea, anorexia and diarrhea may also occur. If treated patients begin to lose more than two pounds weekly for several weeks, aggressive treatment of the above listed adverse effects is indicated.

Vitamin supplementation with a multi-vitamin that does not contain iron is recommended during therapy to ensure appropriate intake as adequate vitamin ingestion may decrease during this time.

Injection Site Reactions

Injection site reactions occur with pegylated interferon and appear to be more common with the use of pegylated interferon alfa 2b. Injection site reactions may appear unsightly, but rarely limit therapy. These reactions can be minimized by applying ice to the injection site prior to injection, allowing the alcohol to dry after cleaning the injection site and ensuring that the interferon is at room temperature immediately prior to the injection. The injection should be given at a 45-90 degree angle. Following the injection, manipulate of the site should be avoided. As pegylated interferon is given once a week, it is helpful to use six to eight different injection sites around the body to minimize the reactions in each given area and allow for adequate healing over time. [60]

Hair Loss

Hair loss may occur on therapy but it is generally mild. Women tend to be more cognizant of mild hair loss than men. Male pattern baldness does not occur as a result of therapy nor does the dramatic hair loss seen in cancer chemotherapy. Rather, hair loss with interferon and ribavirin is usually noticed in the shower or upon manipulation. It is important to understand that hair loss in this situation is temporary and that hair loss will stop and normal hair growth will return upon cessation of therapy. Rarely, hair loss can be the result of the development of

thyroid disease so all patients who complain of hair loss should have thyroid testing performed. Hair loss on therapy can be minimized by cutting hair short, towel drying instead of blow drying, and avoiding the use of harsh chemicals.

Insomnia

One of the most common complaints reported early in therapy is the inability to get a good night sleep and the development of insomnia. This must be addressed early on as persistent lack of sleep can lead to irritability and substantial decreases in overall quality of life. Poor sleep habits may be one of the initial signs of depression and people with insomnia must be evaluated for depression. If there are no signs of depression, the insomnia can be addressed. Good sleep hygiene is essential to getting a good night sleep. Caffeine and alcohol use should be limited as these interfere with the ability to fall asleep or sleep through the night without frequent wake ups. Patients should be counseled to go to sleep only when drowsy and to maintain a regular sleep schedule. Daytime napping should be limited and patients should wind down and relax for about one hour before going to bed. Relaxation techniques such as yoga or biofeedback can be helpful. If these therapies are unsuccessful, pharmacologic therapy may be necessary. Common medications used to aid in sleep include zolpidem, zaleplon and low doses of alprazolam.

Anemia

Ribavirin frequently leads to anemia which can cause fatigue and place a patient at risk for the development of chest pain, shortness of breath and even heart attack. The degree of hemoglobin drop is directly proportional to the ribavirin dose, with many patients having a decrease in hemoglobin by as much as three to four grams within four to eight weeks of starting treatment. In the major clinical studies with pegylated interferon and ribavirin, significant anemia requiring a ribavirin dose reduction occurred in 13-22% of treated patients. [2,60] The current standard of care and approved recommendation for the management of anemia secondary to ribavirin is dose reduction. Patients without a history of heart disease should have their ribavirin dose reduced by 200 mg or one pill if

the hemoglobin falls below 10 grams/dl, and ribavirin must be stopped if the hemoglobin falls below 8.5 grams/dL. In patients with a history of heart disease, ribavirin should be dose reduced if there is a greater than two gram drop in hemoglobin during any four week period on therapy and discontinued if the hemoglobin remains below 12 grams/dL despite dose reduction.[64] Recently, data has suggested that even a small decrease in ribavirin dose may decrease sustained viral response rates in cirrhotic patients with hepatitis C.[67] Therefore, it seems reasonable to use other means to counter the anemia caused by ribavirin and allow for the continuation of ribavirin without dose reduction at the initially recommended doses. This concept has led to the widespread use of erythropoietin as an adjunct therapy, although erythropoietin is not currently approved for use in this indication. Erythropoietin is an injectable medication that has been shown at doses of 40,000-60,000 units per week to increase hemoglobin level in people currently being treated with ribavirin, to allow ribavirin to be used without dose reduction, and to most importantly, relieve the fatigue associated with therapy and dramatically improve patients reported quality of life on therapy.[118]

Neutropenia

Pegylated interferons have been associated with a greater decrease in absolute neutrophil counts than standard interferons, requiring dose reduction secondary to neutropenia in 18-20% of treated patients.[2,60] While neutropenia is common, rarely is the neutropenia severe enough to warrant permanent discontinuation of therapy. If the neutrophil count drops below $0.75 \times 10^9 / L$, the pegylated interferon dose should be reduced by 50%. If the neutrophil count falls below $0.50 \times 10^9 / L$, therapy should be discontinued.[2,60] Neutrophil counts usually return to pretreatment levels within four weeks of stopping therapy. Based upon the concern of neutropenia, many physicians have advocated the use of granulocyte-colony stimulating factor (G-CSF) at a dose of up to 300 ug subcutaneously per week. Currently, there are no clinical trials to demonstrate the effectiveness of G-CSF although clinical experience does support its efficacy in certain situations.

Pulmonary

Pulmonary conditions such as shortness of breath or cough may develop on combination therapy. If cough develops, patients should be evaluated for such conditions as pneumonia or pulmonary fibrosis. Assuming no other cause of cough is found, increasing fluid intake, avoidance of environmental irritants such as cigarette smoke, use of a humidifier, and the use of cough drops or non-sedating cough medications may help to alleviate this annoying symptom. Shortness of breath is another symptom which can occur on combination therapy. If shortness of breath occurs, anemia must be evaluated for as ribavirin can cause significant and life threatening anemia. If shortness of breath occurs in the absence of anemia, other lung conditions such as pneumonia, interstitial pneumonitis and sarcoidosis must be looked for. [56,57]

Thyroid

Pegylated interferon therapy may cause or aggravate the thyroid resulting in either the development of hypothyroidism or hyperthyroidism. Thyroid studies should be checked periodically while on therapy and in the six months following therapy. The use of thyroid replacement hormones to treat symptomatic hypothyroidism while on antiviral therapy is not uncommon. Thyroid dysfunction as a result of antiviral therapy may be irreversible following cessation of interferon therapy and may require the lifelong use of thyroid replacement hormone in patients with hypothyroidism. [56,57]

Ophthalmologic

Complaints related to the eye are being more widely reported with the widespread use of pegylated interferons and ribavirin. People with pre-existing eye problems such as retinopathy, especially people with diabetes and hypertension, should receive periodic eye examinations prior to and during therapy. Any complaints of blurry vision, floaters or loss of vision should be evaluated immediately as retinal artery and central vein thrombosis, retinal hemorrhages, optic neuritis and papilledema may by induced or aggravated by interferon therapy. [56,57]

Neuropsychiatric Side Effects

Neuropsychiatric side effects are commonly seen with the use of pegylated interferon and ribavirin. The most common reason for premature discontinuation of pegylated interferon and ribavirin therapy for hepatitis C is the development of neuropsychiatric symptoms such as depression. The incidence of depression described with combination pegylated interferon and ribavirin ranges between 21-31%.[2,60] Signs and symptoms of depression are usually noted in the first three months of therapy although these symptoms may occur at any time during therapy. Depression may manifest as a spectrum of findings including insomnia, irritability, impaired concentration, change in eating habits resulting in either weight gain or loss, loss of interest in sex, and the inability to get pleasure from things previously enjoyed. Therefore, it is important to conduct routine assessments for depression throughout the entire course of therapy.

Depression is best managed with a combination of therapy with a trained mental health professional and with the use of anti-depressant medications. The most popular class of anti-depressants used by hepatitis C treating physicians is the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, sertraline, paroxetine, and citalopram. Once recognized, depression should be treated as early as possible, as SSRIs take several weeks to become effective.

Miscellaneous

Several other conditions have been reported with the use of pegylated interferons. Ulcerative, hemorrhagic and ischemic colitis have been observed with twelve weeks of initiating therapy and typically present with abdominal pain, bloody diarrhea and fever. Pancreatitis has also been reported. If these conditions occur, therapy should be stopped immediately and the patient referred to the appropriate physician. [56,57]

New York State Department of Health
Policy Statement and Guidelines to Prevent Transmission of HIV and Hepatitis B through Medical/Dental Procedures

Background

All medical and scientific data confirm that the risk of transmission of human immunodeficiency virus (HIV) and hepatitis B (HBV) through medical/dental procedures is remote and largely preventable through strict adherence to barrier precautions and infection control practices that decrease the opportunity of blood-to-blood exposure for both healthcare personnel and patients.

After more than 10 years of experience and millions of procedures, there is still only one documented case in which a healthcare worker with HIV transmitted the virus to patients. Ongoing and completed studies involving more than 15,000 patients of healthcare personnel infected with HIV, including surgeons and dentists, have revealed no infection of patients through medical procedures. Evaluation of AIDS cases that have no identified risk also has not implicated an infected healthcare worker in transmission.

The risk of hepatitis B virus (HBV) transmission through medical/dental procedures is several times greater than HIV. Twenty dusters of hepatitis B transmission to patients have been reported and investigated over the past 20 years. These cases commonly involved a breakdown in infection control during procedures where the healthcare worker's hands were within a body cavity and injury to the worker caused bleeding into the patient. Most reported dusters of hepatitis B in the U.S. occurred prior to 1985. The decrease in such reports in recent years may reflect the adoption of universal precautions and increased use of hepatitis B vaccine among healthcare workers.

Since the advent of the AIDS epidemic, both the Centers for Disease Control (CDC) and the New York State Department of Health have issued recommendations to healthcare workers and healthcare facilities emphasizing the importance of strict adherence to infection control standards and universal barrier precautions to minimize exposure to bloodbome pathogens in medical/dental settings.

In January 1991, the Department of Health issued a policy statement and guidelines concerning HIV-infected medical personnel. This policy emphasizes voluntary testing of healthcare workers and case-by-case evaluation of HIV-infected personnel who perform invasive procedures to determine if they pose a significant risk to patients. The policy states that HIV infection alone is not sufficient justification to limit the professional duties of healthcare professionals unless specific factors compromise a worker's ability lo meet infection control standards or to provide quality patient care.

In July 1991, the CDC issued 'Recommendations for Preventing the Transmission of HIV and Hepatitis B to Patients During Exposure-prone Invasive Procedures." In September, Congress passed a law directing all states to adopt the CDC recommendations or equivalent standards.

These actions prompted the New York State Department of Health to again review all scientific and medical data bearing on the risk of HIV transmission through medical/ dental procedures. In conducting this evaluation, the department consulted widely with infection control experts and with representatives of medical, dental and hospital associations, and consumer groups.

On October 8, 1991, the department issued for public comment a proposed "Policy Statement and Action Plan to Prevent Transmission of HIV through Medical/Dental Procedures." The document reaffirmed the state's existing HIV-

prevention/protection policies. It also outlined proposed state initiatives to strengthen infection control training and practice for healthcare practitioners. A total of 36 interested groups or individuals representing a broad range of interests provided written comment or testified at a public hearing held on November 4, 1991. The overwhelming majority of those providing comment endorsed the state's policy and action plan; some also provided specific suggestions for modifications or adjustments.

On August 11, 1992, Governor Cuomo signed legislation that formally codifies New York's policies and guidelines to protect all citizens from exposure to HIV, HBV and other bloodbome pathogens during medical/dental procedures, and to safeguard the rights of infected workers.

August 1992 —FINAL

Policy Statement

Based on evaluation of all available medical and scientific data, the Department of Health believes the following HIV and HBV-related policies best safeguard New York's citizens and protect the viability of our healthcare system.

1. The most effective means of preventing HIV and HBV transmission in healthcare settings is through strict adherence to universal barrier precautions and established infection control practices which decrease the opportunity of direct exposure to blood and body fluids for both workers and patients.

2. Voluntary testing without fear of disclosure or discrimination is the best means of encouraging people at risk for HIV or HBV to seek counseling and testing.

3. All patients and healthcare personnel who have been potentially exposed to HIV or HBV through personal risk behavior, blood products or occupational accidents should be strongly counseled to seek testing so they may benefit from medical management

4. Mandatory HIV screening of New York healthcare workers would cost millions of dollars and would not produce any appreciable gain in public safety. A negative antibody test does not rule out the presence of infection since it can take some time for measurable antibodies to appear.

5. HIV or HBV infection alone does not justify limiting a healthcare worker's professional duties. limitations, if any, should be determined on a case-by-case basis after consideration of the factors that influence transmission risk, including inability or unwillingness to comply with infection control standards or functional impairment which interferes -with job performance.

6. Requiring healthcare workers to inform patients or employers that they are HIV or HBV positive would only serve as a deterrent to workers seeking voluntary testing and medical evaluation. It also would endanger the professional careers of competent and needed health personnel who pose no risk to patients.

Guidelines

In its ongoing evaluation of the risk associated with potential exposure to HIV and HBV in healthcare settings, the Department of Health has identified measures the state can take to enhance public safety and to guard against discrimination for HIV- or HBV-infected healthcare personnel.

1. *Mandatory Infection Control Training for Healthcare Personnel*

New York State has been in the forefront of promoting infection control training and practice to prevent bloodborne disease exposure to healthcare workers or patients. All hospitals are required by regulation to train their staffs in infection control techniques, to provide appropriate equipment and to enforce use of universal barrier precautions in'situations involving potential exposure to blood or other body fluids. The department also has provided detailed infection control guidelines to all physicians and dentists practicing in New York State.

To increase public safety, New York State has passed legislation to require licensed healthcare professionals (including physicians, physicians' assistants, specialists' assistants, registered nurses, licensed practical nurses, dentists, dental hygenists, podiatrists, optometrists) to complete a course in infection control and barrier precautions on or before July 1, 1994, and every four years thereafter. Required courses, tailored to the infection control training needs of specific medical and dental specialties, will include work practices and engineering controls, disinfection and sterilization procedures. Course content must be approved by the State Department of Health and/or Education.

Proof of completion of required infection control training must be submitted by health professionals to either the State Department of Health or the Education Department. Physicians with hospital privileges will present the necessary training documentation to the hospital (in lieu of the Department of Health) during the process of renewing hospital privileges. A waiver of this training requirement may be granted by the Department of Health to health professionals who demonstrate that such training is not needed due to the nature of their work, or that they have met criteria for equivalency.

2. *Enforcement of Infection Control Standards*

All licensed healthcare facilities are responsible under existing regulations for monitoring and enforcing proper use of infection control practices and universal precautions by healthcare personnel functioning under their jurisdiction. Failure to comply with this requirement will result in Department of Health citation, potential fines and other disciplinary action against the institution.

Any licensed healthcare professional who fails to use appropriate infection control techniques to protect patients or fails to ensure that healthcare workers under his/her supervision do so may be subject to charges of professional misconduct and disciplinary action.

Any patient or employee complaint regarding lax infection control practices in a private medical or dental office will prompt an investigation by the departments of Health and/or Education. Substantiated lapses in infection control in a private practice setting may result in charges of professional misconduct against any licensed professional in the practice who was directly involved, was aware of the violation or who has responsibility for ensuring that office staff are adequately trained and follow patient protection measures.

The state departments of Health and Education will promulgate regulations and/or statutory amendments to implement these more stringent enforcement provisions.

3. *Protecting Healthcare Workers from Infection*

Each healthcare facility should take the following steps to protect workers from occupational exposure to HIV, HBV and other bloodborne pathogens.

1. All healthcare workers should receive appropriate training for their job titles in infection control techniques, including engineering and work practice controls, universal precautions and work practices that help prevent needle-sticks or other injuries and splashes of blood and body fluids.

2. All healthcare personnel should be provided a safe work environment, including protective equipment, clothing and devices to reduce the risk of occupational exposure to blood and body fluids.

3. All healthcare workers whose job responsibilities involve contact with blood or sharp objects likely to be contaminated with blood should be offered and encouraged to receive the hepatitis B vaccine.

4. All healthcare personnel should receive information about the risks associated with HIV and HBV transmission and the merits of knowing their status if they have personal or occupational risks so they may benefit from medical management.

5. All healthcare workers should be informed that if they have an impaired immune system due to HIV infection or other medical condition, they are at risk of acquiring potentially life-threatening infections, including TB, from patients.

6. Information on the availability of voluntary, confidential or anonymous counseling and testing for HIV and HBV should be made available to healthcare workers.

4. Process for Evaluating Infected Healthcare Workers

To ensure that public protection is a primary consideration and that healthcare personnel are afforded appropriate and equitable treatment, the Department of Health will establish a uniform process and criteria for evaluating HIV/HBV-infected healthcare workers to determine if practice limitations are warranted.

Evaluation Criteria

The evaluation of a healthcare worker should be based on the premise that HIV or HBV infection alone is not sufficient justification to limit a healthcare worker's professional duties. The determination of whether an individual healthcare worker poses a significant risk to patients which warrants job modification, limitation or restriction requires a case-by-case evaluation which considers the multiple factors that can influence risk. Periodic re-evaluation of an HIV-infected healthcare worker may be appropriate if physical or mental functioning changes due to disease progression.

Factors that may have a bearing on the ability of healthcare workers, including those with bloodborne infections, to provide quality healthcare include:

- physical or mental condition that may interfere with the worker's ability to perform assigned tasks or regular duties;

- lack of compliance with established guidelines to prevent transmission of disease and/or documentation or evidence of previous transmission of bloodborne pathogens;

- the appropriateness of techniques as related to performance of procedures; any health condition that would pose a significant risk to others.

Institutional Review Process

Under State Health Department regulations, all licensed healthcare institutions are responsible for ensuring that their employees, medical staff and volunteers do not have physical or mental impairments related to HIV or HBV infection or any other condition that would interfere with the performance of their duties or pose a risk to patients.

Consistent with this regulation, healthcare facilities are responsible for establishing a mechanism for evaluating healthcare workers with HIV or HBV infection. This requirement should not be misconstrued to foster or condone involuntary screening of employees for HIV or HBV by healthcare institutions.

New York State law prohibits HIV testing of any citizen without written, informed consent. All healthcare workers should be counseled about the importance of learning their HIV and HBV status if they have been potentially infected through personal behavior or occupational exposure.

Institutional evaluations of individual workers known to be infected with HIV or HBV shall be based on the Department of Health criteria, and shall involve consultation with experts who can provide a balanced perspective. Such experts include an infectious disease physician and/or hospital epidemiologist with an understanding of HIV and HBV, a representative from the infected healthcare worker's practice area and the personal physician of the infected worker. All matters related to such evaluations must be handled confidentially.

Any modification of work practice must seek to impose the least restrictive alternative in accordance with federal disability laws. Any worker who believes that his/her employment has been restricted or terminated without just cause may ask for a second opinion from a Department of Health review panel and/or file a complaint with the State Human Rights Commission.

State-Appointed Review Panels

The State Health Department will establish and oversee a voluntary evaluation process to provide guidance to HIV/ HBV-infected healthcare workers who seek consultation. Access to state-appointed panel review will be available to infected healthcare workers who perform procedures that might increase the risk of worker-to-patient blood exposure. State panels will function as a primary evaluation resource for practitioners who are not affiliated with institutions, or as a second opinion for workers affiliated with health facilities who have been evaluated by their institutions.

Each panel will include a public health official, an infectious disease expert, an expert in infection control/ epidemiology. In addition, an individual from the infected practitioner's area of practice and the individual's private

physician may be asked to serve as members of the panel.

The purpose of such panels is to provide timely advice and consultation on an individual's risk of bloodborne disease transmission through his/her professional practice, and to recommend practice limitations, modifications or restrictions where the evidence suggests there is a significant risk to patients.

The evaluation process will be confidential except for the following circumstances:

- To adequately evaluate workers who are institutionally based, the panel — directly or through its designees — may need to request information about the worker's practice from the facility.

- If practice restrictions are recommended, the individual involved shall assure — and verify to the panel — that all health facilities where he/she practices are informed. If assurance is not forthcoming, the panel will inform such facilities. Within all facilities, the normal rules of confidentiality apply.

DOH Consultation

Staff of the Department of Health will be available to any individual, institution or organization to discuss concerns about the management of employees with HIV or HBV. In addition, the department will provide information, confidentially or anonymously, on the process for accessing the state review panels described above.

Enforcement of Practice Restrictions

Healthcare institutions will be responsible for ensuring that any practice limitations recommended by institutional panels are followed in the facility by healthcare workers who are in their employ or who provide patient care from their facilities. If practice limitations are recommended for a community-based physician or dentist, periodic monitoring to ensure compliance will be performed by the State Department of Health or Education with the professional's consent. If a healthcare professional does not follow the practice

restrictions or if compliance is uncertain, the appropriate state licensing/certification/permit board will be notified. The professional may be' charged with professional misconduct for negligent practice in violation of the State Education Law.

Confidentiality of a Healthcare Worker's HIV Status

HIV-infected healthcare workers are entitled to protections under the New York State HIV Confidentiality Law as are all citizens. Such workers are not required to disclose their HIV status to patients or employers. Healthcare facilities are under no obligation under New York law to disclose to patients the status of an infected healthcare worker in their employ; such disclosure, without the consent of the worker, would likely violate New York's HIV Confidentiality Law.

Notification of patients that they were exposed to the blood of a healthcare worker should be based on documentation of an injury to a worker that could have resulted in the worker's blood coming into direct contact with a patient's bloodstream or mucous membranes. In such circumstances, the patient should be advised to receive testing for potential HIV or HBV exposure. The Department of Health will be available to assist hospitals in determining if a significant risk of exposure to bloodborne pathogens warrants notification to patients.

5. Quality Assurance Protections

1. Hospital quality assurance programs, and under their umbrella, infection control policies and procedures, are key mechanisms for preventing disease transmission within healthcare settings. To further reduce the low risk of HIV or HBV transmission through medical procedures, hospitals should take the following actions:

2. Assure that infection control policies and procedures for the prevention of bloodborne infections are in place and being monitored for compliance.

3. Review existing policies and procedures to assure that mechanisms are in place for reporting and managing circumstances where an employee is exposed to a patient's blood or there has been mutual blood exposure between a patient and employee (i.e., during a procedure where injury to a worker resulted in both parties having contact with the other person's blood).

4. Form cooperative work groups to review surgical techniques to identify changes in practice or other alternatives to reduce any risk of potential injury to a healthcare worker that could result in blood exposure to patients.

Internet Resources

The National Academy of Clinical Biochemistry. Laboratory Medicine Practice Guidelines. Laboratory Guidelines For Screening, Diagnosis And Monitoring Of Hepatic Injury (2000)
https://www.aasld.org/eweb/DynamicPage.aspx?Site=AASLD3&webcode=ViralHepatitis

Department of Veterans' Affairs (VA) Guidelines (April 2003)
http://www.hepatitis.va.gov/vahep?page=tp03-01-04-01

Centers for Disease Control and Prevention. National Hepatitis C Prevention Strategy 2001.
www.cdc.gov/ncidod/diseases/hepatitis/c/plan/index.htm

Centers for Disease Control and Prevention. Hepatitis C. Sexually transmitted diseases treatment guidelines. MMWR 2002;51(RR-6): 64-6.
www.cdc.gov/mmwr/preview/mmwrhtml/rr5106a1.htm

Centers for Disease Control and Prevention. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis, MMWR 2001;50(No. RR-11):1-42.
www.cdc.gov/mmwr/preview/mmwrhtml/rr5011a1.htm

Centers for Disease Control and Prevention. Prevention and Control of Infections with Hepatitis Viruses in Correctional Settings. MMWR 2003. 52(RR01);1-33.
www.cdc.gov/mmwr/preview/mmwrhtml/rr5201a1.htm

National HCV Prison Coalition. Includes state-by-state guidelines.
www.hcvinprison.org/new/state_guidelines.html

The National Center for Complementary and Alternative Medicine
http://nccam.nih.gov/clinicaltrials/

Hepatitis C and injection drug use
www.cdc.gov/idu/hepatitis/viral_hep_drug_use.htm

New York State Department of Health HIV Guidelines
www.hivguidelines.org

New York State Expanded Syringe Access Program, including participating pharmacies and healthcare facilities
www.health.state.ny.us/nysdoh/hivaids/esap/regover.htm

Information regarding NYS syringe exchanges may be found at:
www.health.state.ny.us/nysdoh/hivaids/esap/provdirect.htm

British Society of Gastroenterology (Includes addendum incorporating use of pegylated interferon, 2003)
www.bsg.org.uk/clinical_prac/guidelines/hep_c.htm

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